

U.S. Patent Application No. 10/087,987

Election dated March 21, 2005

Reply to Restriction Requirement of October 20, 2004

Attorney Ref. No.: 082137-0280712

II. ELECTION WITH TRAVERSE

In response to the requirement for restriction and election mailed October 20, 2005, the applicants elect **with traverse** the invention of group 10, directed to a method for treating a malignancy wherein the administered agent directly blocks the activity of active matriptase in an epithelial tissue.

In response to the requirement to elect between antibodies M69 and M123, the applicants elect antibody M69 **with traverse**.

Traverse

A. Restriction between blocking matriptase activity in epithelial and non-epithelial tissues

The applicants respectfully traverse the requirement for restriction between the disclosed method of treatment wherein matriptase activity in an epithelial tissue is blocked, and the disclosed method wherein matriptase activity in a non-epithelial tissue is blocked.

The distinction between treatment by inhibiting matriptase activity in an epithelial tissue versus in a non-epithelial tissue that is made in the restriction requirement is in contradiction to the physiological presence of matriptase in both epithelial and non-epithelial tissues of a human patient that is typically treated by the claimed invention. The application teaches that matriptase is produced by epithelial-derived cells (for example, see paragraphs 4 and 48-49); however, matriptase is also produced by non-epithelial cells such as endothelial cells of developing vasculature (see Aimes et al., "Endothelial cell serine proteases expressed during vascular morphogenesis and angiogenesis," 2003, *Thromb. Haemost.* 89:561-72; and Oberst et al., "Characterization of matriptase expression in normal human tissues, 2003, *J. Histochem. and Cytochem.*, 51(8):1017-25, copies attached). Moreover, active matriptase protease molecules may be shed by cells of one type of tissue, e.g., epithelial cells (for example, see paragraph 83), and such shed matriptase molecules can diffuse into different types of tissues, e.g., into stromal tissue, which is in close association with epithelial tissue in many types of malignant and pre-malignant lesions (for example, see Ibe et al., "Tumor Rejection by Disturbing Tumor Stroma Cell Interactions, 2001, *J. Exp. Med.*, 194(11):1549-1560, copy attached). Active matriptase may be released into non-epithelial tissues by epithelium-derived pre-malignant or malignant cells that have penetrated into non-epithelial tissues as a result of invasion or metastasis. The successful operation of the claimed invention includes detecting and inhibiting the activity of matriptase in non-epithelial tissues as well as in epithelial tissues of a patient's pre-malignant or malignant lesions. There is no

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physiological or medical basis for classifying the claimed method on the basis of whether the agent that is administered blocks the activity of active matriptase in an epithelial versus in a non-epithelial tissue. Moreover, prior art that is relevant to the claimed invention is unlikely to distinguish between the detection and inhibition of matriptase in epithelial tissues versus in non-epithelial tissues. Therefore, little or no additional burden would be imposed by removing the restriction of the claimed method based on the type of tissue in which matriptase activity is inhibited. In view of the foregoing, the applicants respectfully request that the requirement to elect between inhibition of matriptase in epithelial tissues versus non-epithelial tissues be withdrawn.

B. Restriction between treatment with anti-matriptase antibodies M69 and M123

The restriction requirement further calls for election between disclosed antibodies M69 and M123 (see p. 12). The applicants respectfully traverse the requirement for restriction between using antibody M69 and using antibody M123 in practicing the claimed method. The application discloses that it is possible to prepare antibodies that are capable of binding specifically to an active form of matriptase without recognizing the inactive form of matriptase (*e.g.*, see p. 9, paragraph 23). In fact, the applicants prepared and identified at least three different antibodies that specifically recognize the active form but not the inactive form of matriptase, two of which antibodies (M69 and M123) are disclosed in the present application. In addition, the application describes using such antibodies that specifically recognize the active form of matriptase to detect the presence of the active form of matriptase in pre-malignant or malignant lesions (*e.g.*, see p. 3, paragraph 7). The application thus enables persons of skill in the art to make, identify, and use antibodies other than M69 and M123 that bind specifically to active but not inactive matriptase and are suitable for use in the elected method, and the independent claims are not directed to a method which relies upon a specific antibody. In addition, the search that is required to identify prior art relevant to practicing the elected invention as practiced with either one of M69 or M123 would also identify the prior art relevant to practicing the elected invention with the other antibody, so that withdrawal of the requirement for election of a single antibody would not result in an additional burden in searching for prior art. Accordingly, the applicants respectfully request that the requirement to elect between the claimed invention as practiced with either antibody M69 or antibody M123 be withdrawn.

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C. Restriction between malignant and pre-malignant conditions

The applicants respectfully traverse the requirement for restriction between the treatment of pre-malignancies and the treatment of malignancies by the method of claim 16. Persons of skill in the art of detecting and treating cancer recognize that pre-malignant and malignant lesions represent states on a common continuum constituting the accumulation of genetic and biochemical alterations that are characteristic of cancer development (e.g., see Bocchetta et al., *Oncogene*, 2004, 23(38):6484-6491; and Barrett, *Environ Health Perspect.*, 1993, 100:9-20, abstracts attached). A detailed description of the genetic and biochemical, as well as physiological alterations and that are common characteristics of both pre-malignant and malignant lesions is found in Silverstein, M.J. (ed) Ductal Carcinoma in Situ of the Breast, 2nd Ed. Lippincott, Williams and Wilkins, Philadelphia, 2002 (textbook, not enclosed). The same kinds of assays are typically used to detect physiological and molecular alterations characteristic of both pre-malignant and malignant lesions of a given type of cancer (e.g., see Yang et al., *Cancer*, 2002, 94(9):2380-92; and Haimov-Kochman et al., *Harefuah*, 2002, 141(8):702-708, abstracts attached; and Silverstein MJ (ed), Ductal Carcinoma in Situ of the Breast, 2nd Ed, cited above). Likewise, the same agents and methods that are used to treat malignancies are also used to treat pre-malignancies, e.g., tamoxifen and pan-EGF inhibitor, and surgical excision. Accordingly, the search that is performed to identify prior art relating to using an agent that blocks the activity of active matriptase to treat malignancies would also identify the prior art relating to the treatment of pre-malignancies, and vice-versa. Given the commonality of the molecular and physiological characteristics of pre-malignant and malignant lesions and the use of the same methodologies to detect and treat both, and given that a search of the claimed invention for treating one would also be expected to identify the prior art relating to the other, as discussed above, the applicants respectfully request that the restriction of the claimed method separating treatment of pre-malignant and malignant lesions be withdrawn.

If the restriction between treatment of pre-malignant and malignant lesions is withdrawn, the applicants further elect in response to the additional requirements stated on pages 8-9 of the official action, a pre-malignant condition that involves tissue remodeling, which condition is atypical ductal hyperplasia of the breast.

The requirement to elect between pre-malignant conditions that involve (a) tissue remodeling, (b) inflammatory responses, and (c) smooth muscle proliferation is traversed because pre-malignant conditions commonly involve combinations of two or all three of these indications. Persons of skill in the art would generally expect that a pre-malignant

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condition that is treated by the claimed method would involve two or all three of the specified indications, and that a search of prior art relating to any of the three specified indications would also be expected to identify references that relate to the others.

The requirement to elect between the pre-malignant conditions listed on pages 8-9 of the official action is traversed because the all of the disclosed conditions have in common an association with expression of active matriptase, and the steps of the claimed method are the same for each condition. Therefore, a single search rather than a separate search for each condition would reasonably be expected to identify the prior art relevant to the claimed invention, and withdrawal of the requirement for election of a specific pre-malignant condition would add little or no additional search burden.

Claim 16 is a linking claim that links groups 10-13

The official action characterized claim 16 as it is drawn to treatment of malignancies as a linking claim that links invention groups 10-13, and stated that:

“upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all of the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.”

See page 5 of the official action. In accord with the foregoing, and if the stated restrictions are maintained, the restriction requirement as to the linked inventions of groups 10-13 shall be withdrawn upon the allowance of the linking claim, and claims directed to the claimed method comprising (a) administering an agent which blocks the activity of active matriptase in a tissue other than an epithelial tissue, and (b) administering an agent which blocks the activity of an agent that induces the activation of matriptase, will be entitled to examination in the instant application.

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III. REMARKS

Claims 16-26 are withdrawn, claims 1-15 and 27-33 are canceled, and new claims 34-50 are submitted.

The subject matter of new claims 34-50 corresponds to that of elected group 10, claims 16-17 and 20-22 (withdrawn), and is supported by the description of the invention in the written description, including the original claims.

IV. IN CONCLUSION

If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully Submitted,

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